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ORIGINAL ARTICLE

A convenient and efficient synthesis of thiazolidin-4-ones *via* cyclization of substituted hydrazinecarbothioamides

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Hydrazinecarbothioamides;
Dimethyl acetylenedicarboxylate;
Thiazolidin-4-ones;
X-ray crystallography

Abstract 2-Substituted hydrazinecarbothioamides and *N*,2-disubstituted hydrazinecarbothioamides react in high yield with dimethyl acetylenedicarboxylate (DMAD) to give 4-oxo-*Z*-(thiazolidin-5-ylidene) acetate derivatives. Several mechanistic options involving interaction are presented. The structures of thiazolidin-4-ones have been unambiguously confirmed by single crystal X-ray crystallography.

1. Introduction

The reaction of hydrazinecarbothioamides with tetracyanoethylene, 3-(dicyanomethylene)-2-indolone and benzo- as well as naphthoquinones is a convenient method for the synthesis of various heterocyclic compounds, such as pyrazolo[1,2-*c*]-1,3,4-thiadiazoles (Hassan et al., 2003), spiro(indolone-3,2′-[1,3,3]thiadiazole)-2-ones (Hassan et al., 2011), indazoles (Hassan et al., 2007) and thiadiazines (Hassan et al., 2007), respectively.

Acetylenedicarboxylates can be used as Michael acceptor and reacted with various nucleophiles containing sulfur and nitrogen atoms such as thiourea derivatives leading to formation of substituted thiazoles, 1,3-thiazolidin-4-ones and thiazine-4-ones (Gao, 2010; Castagnolo et al., 2009; Imrich et al., 2010; Böhm et al., 2009; Ahmadi et al., 2009).

Thiazoles are synthetic intermediates and common substructures in numerous biologically active compounds (Sun et al., 2008; Miwatashi et al., 2005; Pereira et al., 2006; Wang et al., 2005; Lentzen et al., 2003; Yavari et al., 2007). Owing to the various physiological activities of thiazolidinones, many thiazolidinone derivatives have been prepared and

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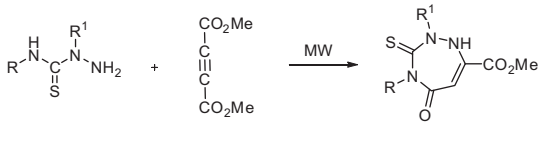
several new methods for the preparation of substituted thiazolidin-4-ones have been reported (Yavari et al., 2007; Sunduru et al., 2009). Thiazolidin-4-one compounds, display anti-microbial (Aridoss et al., 2009), anti-mycobacterial (de Aquino et al., 2008), anti-HIV (Rawal, 2007), anti-inflammatory (Ottaná et al., 2005), and anti-cancer activities (Vicini et al., 2003).

1,3-Thiazolidin-4-ones were observed as the only product during the reaction of thiosemicarbazide and thiosemicarbazone derivatives with acetylenedicarboxylates (Yavari et al., 2007; Aly et al., 2010, 2014; Hassan et al., 2012, 2014a,b). One-pot three component reactions containing diethyl acetylenedicarboxylate, thiosemicarbazones and arylidenemalononitrile afforded thiazolidine derivatives (Aly et al., 2014). Also, the reaction of 4-phenylthiosemicarbazide, dimethyl acetylenedicarboxylate (DMAD) in the presence of aldehydes and ketones gave thiazolidine-4-ones (Yavari et al., 2007). Treatment of diacylthiosemicarbazides (Aly et al., 2010), 1,4-thiosemicarbazides (Hassan et al., 2014a) and thiocarbohydrazides (Hassan et al., 2012, 2014b) with DMAD afforded thiazolidine-4-one derivatives.

Methyl [3-aryl-4-oxo-1-(phenylthiocarbamoyl)-4,5-dihydro-pyrazol-5-ylidene]ethanoates were formed from the reaction of arenealdehyde 4-phenylthiosemicarbazones with dimethyl acetylenedicarboxylate (DMAD, **2**) (Hassan et al., 2008), whereas 1,2,4-triazepine-3-thiones **3a–g** were formed *via* conventional and microwave irradiation of 4-substituted thiosemicarbazides **1a–c** and 2,4-disubstituted thiosemicarbazides **1d–g** with (DMAD, **2**) (Scheme 1) (Aly et al., 2008).

2. Result and discussion

We report here the results of our investigations on the reaction of 1-substituted and 1,4-disubstituted thiosemicarbazides **4a–e**



1a-g **2** **3a-g**

1. 3:a, R = C_6H_5, R^1 = H; **b**, R = C_6H_5-CH_2, R^1 = H;
c, R = CH_2=CH-CH_2, R^1 = H; **d**, R = R^1 = C_6H_5;
e, R = C_6H_5-CH_2, R^1 = C_6H_5; **f**, R = C_6H_5-CH_2, R^1 = 4-CH_3-C_6H_4;
g, R = C_6H_5, R^1 = 4-Cl-C_6H_5

Scheme 1 Reactions of hydrazinecarbothioamides **1a–g** with dimethyl acetylenedicarboxylate **2**.

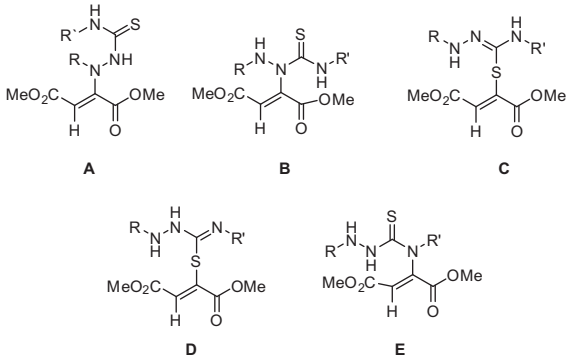


Fig. 1 Expected intermediates (1:1) (**A-E**) through interactions between **4a–e** and **2**.

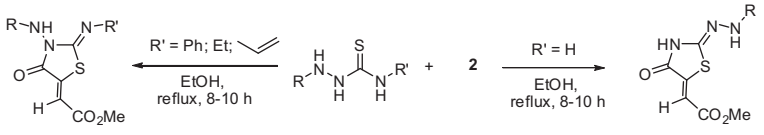
with **2**. These results are compared with those obtained in Scheme 1 (Aly et al., 2008). As shown in Scheme 2, the synthesis of thiazolidin-4-ones **5** and **6** was simply affected by the nucleophilic active centers in hydrazinecarbothioamides **4a–e** and an electrophilic acetylenic ester (DMAD, **2**). The reaction proceeds smoothly without using any catalyst by treatment of **4a–e** with one molar equivalent of dimethyl acetylenedicarboxylate (DMAD, **2**) in ethanol at reflux resulting in the formation of single products **5a**,**b** and **6a–c** in 78–89% yield (Scheme 2).

Elemental analyses and mass spectra clearly revealed that the products were formed by the addition of equimolar of (DMAD, **2**) and **4a–e** with elimination of one molecule of methanol. There are possibilities for the formation of various isomers which would behave spectroscopically very similar. Hydrazinecarbothioamides, N^1, N^2, N^4 and sulfur atom are the nucleophilic sites in compounds **4a–e**.

Thus, several options for the interaction between **4a–e** and **2** may be envisaged. It is probable that all the products observed are formed from one of the five labile (1:1) intermediates (**A–E**) (Fig. 1).

To elucidate the tautomeric states and structure of the products as well as to characterize the products, we use IR, ^{1}H NMR and ^{13}C NMR as well as mass spectrometry. Rigorous structure proof comes from the single crystal X-ray structural analyses of **5b** (Fig. 2) and **6b** (Fig. 3).

To illustrate the structure elucidation of compound **5a**,**b** we choose **5b**, IR spectrum showed two carbonyl absorption bands at 1745 and 1685 (C=O) and a band at 1615 cm^{-1} that assigned to C=N vibration. Broad bands at 3310, 3160 cm^{-1} are due to NH-groups.



6a-c 78-84% **4a-e** **5a,b** 82-89%

4: a, R = C_6H_5, R' = H; **b**, R = O_2S-C_6H_4-CH_3, R' = H;
c, R = R' = C_6H_5; **d**, R = C_6H_5, R' = C_2H_5;
e, R = C_6H_5, R' = CH_2=CH-CH_2
5: a, R = C_6H_5, R' = H; **b**, R = O_2S-C_6H_4-CH_3, R' = H;
6: a, R = R' = C_6H_5; **b**, R = C_6H_5, R' = C_2H_5;
c, R = C_6H_5, R' = CH_2=CH-CH_2

Scheme 2 Reactions of hydrazinecarbothioamides **4a–e** with dimethyl acetylenedicarboxylate **2**.

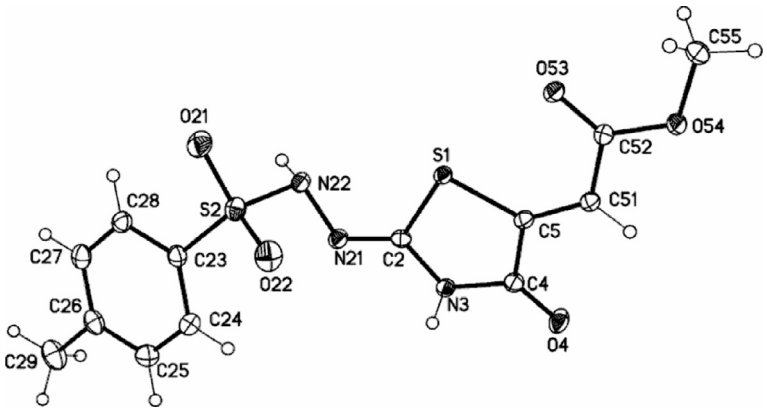


Fig. 2 Molecular structure of **5b** in the crystal (displacement parameters are drawn at 50 % probability level). The crystallographic numbering does not reflect the systematic IUPAC numbering.

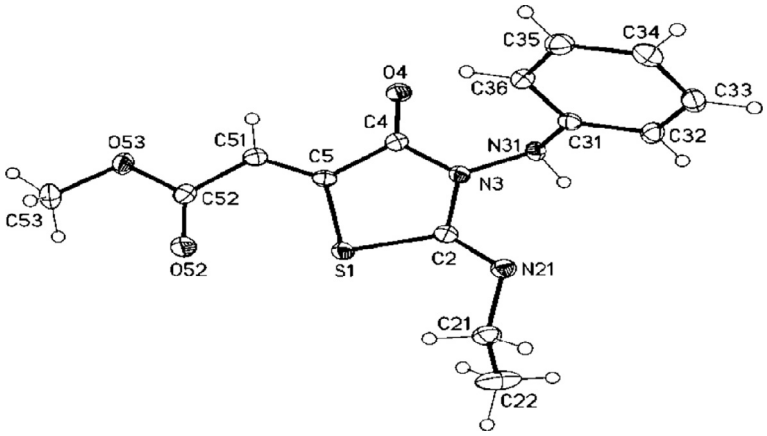


Fig. 3 Molecular structure of **6b** in the crystal (displacement parameters are drawn at 50% probability level). The crystallographic numbering does not reflect the systematic IUPAC numbering.

The ^{1}H NMR spectrum of **5b** showed one methoxy group at δ_H = 3.86, methyl group at δ_H = 2.24 ppm, one phenyl group in the range of δ_H = 6.85–7.24, one vinylic proton at δ_H = 6.85 and NH at δ_H = 8.27. In **5b**, the ^{13}C NMR spectra show five downfield lines at 168.12, 166.64, 145.94, 140.22 and 115.73 ppm, attributed to (C═O, ester), (C-4), (C═N), (C-5) and vinyl-CH, respectively. Full ^{1}H NMR and ^{13}C NMR data are given in the experimental part.

Moreover, the structure of *Z*-methyl-2-[(*Z*)-4-oxo-2-(2-tosylhydrazono)-thiazolidin-5-ylidene]acetate **5b** has been unambiguously confirmed by a single crystal X-ray structure analysis (Fig. 2 and Tables S1–7 in the supplementary data) which confirms a *cisoid* geometry with respect to C═C and C═N double bonds. Also, the vinyl-CH is in *cis* form with the cyclic C═O. The thiazolidine moiety is planar.

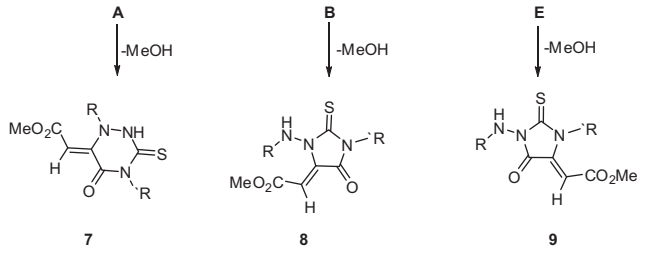
On the other hand, solutions of **4c–e** (1 mmol) in absolute ethanol (15 mL) were added into a solution of **2** (1 mmol) in absolute ethanol (10 mL); the mixture was refluxed for 8–10 h, which later turned into orange precipitates from **6a–c**. The IR spectra of the isolated compounds from the reaction of **2** with **4c–e** showed two carbonyl absorption bands about 1690–1725 cm^{-1}, and a band between 1635 and 1655 cm^{-1} that was assigned to a C═N vibration. A broad band at 3295–3320 cm^{-1} is due to the NH group. The ^{1}H NMR spectrum of **6c** as an example clearly indicated the presence of an allyl group which appeared as three multiplets centered at 4.15, 5.12 and 5.92 ppm due to (allyl-CH_2N), (allyl-CH_2═) and (allyl,—CH═), respectively. The presence of the allyl group was also proved by the ^{13}C-DEPT-NMR spectrum, exhibiting positive signals at 133.72 (allyl-CH═) and negative signal at 45.24 and 117.15 due to (allyl-CH_2N) and (allyl-CH_2═), respectively.

Unambiguous support for these came from the X-ray structure analysis of (*Z*)-methyl-2-[(*Z*)-2-(ethylimino)-4-oxo-3-(phenylamino) thiazolidin-5-ylidene)]acetate **6b** (Fig. 3 and Tables S8–14, in the supplementary data). A *cisoid* geometry with respect to C═C and C═N double bonds and the thiazolidine moiety is planar.

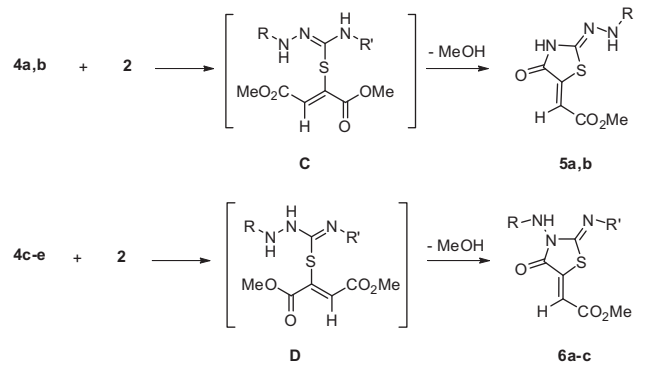
There are possibilities for the formation of various isomers, which would behave very similarly spectroscopically (Schemes 3 and 4). Isomeric products **7–9** (Scheme 3) may be formed as following:

If ^{1}*N*H attacked C/C triple bond of **2**, the intermediate **A** (Fig. 1) could be formed, leading to the product **7** after elimination of a molecule of MeOH (Scheme 3).

The products **8** and **9** (Scheme 3) could be isolated if the reaction involved the addition of thiosemicarbazides —^{2}*N*H or —^{4}*N*H on the C/C triple bond of **2** *via* intermediates **B** or **E** (Fig. 1).



Scheme 3 Formation of various isomers to compounds **5** and **6**.



Scheme 4 The mechanism for the formation of products **5a**, **b** and **6a–c**.

A rationale for the formation of products **5a**,**b** and **6a–c** is depicted in Scheme 4. Nucleophilic attack of SH of **4a–e** on the triple bond of **2** through the intermediate (**C**), followed by intramolecular nucleophilic attack of the NH_2 of **4a**,**b** at α-ester carbonyl group, the products **5a**,**b** would be isolated, where *via* the intermediate (**D**) and nucleophilic attack of SH on the triple bond of **2** with elimination of one molecule of MeOH during the attack of *N*-hydrazinecarbothioamide at the carbonyl ester, the thiazolidin-4-ones **6a–c** would be formed.

3. Conclusion

Reaction of 2-substituted hydrazinecarbothioamides **4a**,**b** and *N*,2-disubstituted hydrazinecarbothioamides **4c–e** with DMAD (**2**) can involve possible competition between nucleophilic addition of several sites (N^1, N^2, N^4 and SH of hydrazinecarbothioamides group) to the triple bond of activated acetylenic ester. Thiaheterocyclic N-C-S + C2 mode of cyclization is favored.

4. Experimental

4.1. Chemistry

All melting points were determined using open capillaries on a Gallenkamp melting point apparatus. The IR spectra were recorded with a Shimadzu 408 instrument using potassium bromide. The 400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR spectra were observed on a Bruker AM 400 spectrometer with tetramethylsilane as the internal standard, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The ^{13}C NMR signals were assigned on the basis of DEPT 135/90 spectra. The mass spectra (70 eV, electron impact mode) were recorded on a Finnigan MAT instrument. Elemental analyses were carried out at the Microanalytical Center, Cairo University, Egypt. Preparative layer chromatography (plc) used air dried 1.0 mm thick layers of slurry applied silica gel (Merck Pf_{254}) on 48 cm wide and 20 cm high glass plates using the solvents listed. Zones were detected by quenching of indicator fluorescence upon exposure to 254 nm light and eluted with acetone.

4.2. Starting materials

2-Substituted hydrazinecarbothioamides **4a**,**b** and *N*,2-disubstituted hydrazinecarbo-thioamides **4c–e** were prepared according to the literature: **4a** (Lee and Lee, 2000), **4b** (Zaharia et al., 2010), **4c** (El-Metwally et al., 2005), **4d** (El-Metwally et al., 2005) and **4e** (Jaźwiński and Staszewska-Krajewska, 2004). Dimethyl acetylenedicarboxylate (DMAD, **2**) was bought from Fluka.

4.3. Products

4.3.1. Reaction of substituted hydrazinecarbothioamides *4a–e* with dimethyl acetylenedicarboxylate (*2*)

A mixture of substituted hydrazinecarbothioamides **4a–e** (1 mmol) and dimethyl acetylenedicarboxylate (**2**) (0.142 g, 1 mmol), in absolute ethanol (30 mL) was refluxed for 8–10 h, cooled to room temperature. Yellow crystals from **5a**,**b** were precipitated, filtered and washed with a small amount of cold ethanol and recrystallized from listed solvents. The reaction mixture between **4c–e** and **2** was pre-concentrated, applied to chromatographic plates and developed using toluene/ethyl acetate (*Qr* = 10:1) to give only one zone containing compounds **6a–c**. The products so obtained were recrystallized.

*4.3.1.1. (Z)-Methyl-2-[(Z)-4-oxo-2-(2-phenylhydrazno)-thiazolidin-5-ylidene]acetate (**5a**, $C_{12}H_{11}N_3O_3S$).* Yellow crystals (0.246 g, 89%), mp. 222 °C (acetonitrile); IR (KBr) *v* = 3288, 3252 (NH), 1692, 1668 (CO), 1640 (C=N), 1605 (Ar—C=C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3H, OCH_3), 6.85 (m, 2H, Ar—H and vinyl-CH), 7.24 (m, 4H, Ar—H), 8.27 (br, s, 1H, NH), 11.27 (br, s, 1H, thiazole-NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.71 (OCH_3), 116.12 (vinyl-CH), 122.81, 127.19, 129.67 (Ar—CH), 140.12 (thiazole-C5), 142.88 (Ar—C), 146.12 (thiazole-C2), 166.73 (thiazole-C4), 168.19 (CO-ester); MS (70 eV): *m*/*z* = 277 (M^+, 100), 246 (12), 218 (19), 145 (22), 105 (39), 92 (54), 77 (62), 65 (42), 59 (21). *Anal. Calcd*: C, 51.98; H, 4.00; N, 15.15; S, 11.56. *Found*: C, 52.11; H, 3.88; N, 15.06; S, 11.74.

*4.3.1.2. (Z)-Methyl 2-[(Z)-4-oxo-2-(2-tosylhydrazono)thiazolidin-5-ylidene] acetate (**5b**, $C_{13}H_{13}N_3O_5S_2$).* Yellow crystals (0.290 g, 82 %), mp. 234 °C (acetonitrile); IR (KBr) *v* = 3310, 3160 (NH), 1745, 1685 (CO), 1615 (C=N), 1590 (Ar—C=C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.24 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.80 (s, 1H, vinyl-CH), 6.90–7.00 (m, 2H, Ar—H), 7.28 (m, 2H, Ar—H), 8.45 (br, s, 1H, NH), 11.16 (br, s, 1H, thiazole-NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.16 (CH_3), 52.75 (OCH_3), 115.73 (vinyl-CH), 129.29, 129.53 (Ar—CH), 138.12 (Ar—C), 140.22

(thiazole-C5), 143.42 (Ar—C), 145.94 (thiazole-C2), 166.64 (thiazole-C4), 168.12 (CO-ester); MS (70 eV): m/z = 355 (M^+, 21), 324 (12), 200 (100), 155 (11), 117 (23), 91 (37). *Anal. Calcd*: C, 43.93; H, 3.69; N, 11.82; S, 18.04. *Found*: C, 44.14; H, 3.78; N, 11.67; S, 17.91.

*4.3.1.3. (Z)-Methyl-2-[(Z)-4-oxo-3-(phenyl-amino)-2-(phenylimino)-thiazolidin-5-ylidene]acetate (**6a**, $C_{18}H_{15}N_3O_3S$)* Pal et al., 2014. Yellow crystals (0.286 g, 81%).

*4.3.1.4. (Z)-Methyl 2-[(Z)-2-(ethylimino)-4-oxo-3-(phenylamino)thiazolidin-5-ylidene]acetate (**6b**, $C_{14}H_{15}N_3O_3S$)*. Yellow crystals (0.256 g, 84%), mp. 151 °C (acetone); IR (KBr): ν = 3310 (NH), 1695, 1725 (CO), 1655 (C═N), 1615 (Ar—C═C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15 (t, 3H, J = 7.6 Hz, CH_3), 3.40 (q, 2H, J = 7.6 Hz, CH_2) 3.85 (s, 3H, OCH_3), 6.50 (s, 1H, vinyl-CH), 6.73 (m, 2H, Ar—H), 6.92 (m, 2H, Ar—H), 7.20 (m, 2H, Ar—H and NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.67 (CH_3), 47.21 (CH_2), 52.65 (OCH_3), 115.05 (vinyl-CH), 116.82, 122.82, 129.23 (Ar—CH), 138.78 (thiazole-C5), 145.16 (Ar—C), 145.77 (thiazole-C2), 162.24 (thiazole-C4), 166.28 (CO-ester); MS (70 eV): m/z = 305 (M^+, 100), 290 (11), 274 (18), 247 (11), 134 (38), 106 (21), 92 (16). *Anal. Calcd*: C, 55.07; H, 4.95; N, 13.76; S, 10.50. *Found*: C, 54.97; H, 5.02; N, 13.85; S, 10.39.

*4.3.1.5. (Z)-Methyl 2-[(Z)-2-(allyimino)-4-oxo-3-(phenylamino)thiazolidin-5-ylidene]acetate (**6c**, $C_{15}H_{15}N_3O_3S$)*. Yellow crystals (0.247 g, 78%), mp. 129 °C (acetone). IR (KBr): ν = 3320 (NH), 1710, 1695 (CO), 1650 (C═N), 1605 (Ar—C═C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 3.88 (s, 3H, OCH_3), 4.15 (m, 2H, allyl-CH_2), 5.12 (m, 2H, allyl-CH_2═), 5.92 (m, 1H, allyl-CH═), 6.60 (s, 1H, vinyl-CH), 6.85 (m, 1H, Ar—H), 7.0 (m, 2H, Ar—H), 7.3 (m, 2H, Ar—H and NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.24 (allyl-CH_2N), 52.61(OCH_3), 115.36 (vinyl-CH), 117.15 (allyl-CH_2═), 122.85, 129.26, 129.26 (Ar—CH), 133.72 (allyl-CH═), 140.51 (thiazole-C5), 141.46 (Ar—C), 145.61 (thiazole-C2), 162.92 (thiazole-C4), 166.56 (CO-ester); MS (70 eV): m/z = 317 (M^+, 100), 286 (13), 258 (9), 225 (14), 92 (33). *Anal. Calcd*: C, 56.77; H, 4.76; N, 13.24; S, 10.10. Found: C, 56.89, H, 4.68; N, 13.12; S, 10.24.

*4.4. Single crystal X-ray structure determination of **5b** and **6b***

Suitable crystals were obtained by recrystallization from acetonitrile. The single crystal X-ray diffraction study was carried out on a Bruker-Nonius ApexII diffractometer at 123(2) K (**5b**) or a Bruker Apex Duo at 120(2) K (**6b**) using MoKα radiation (λ = 0.71073 Å). Direct Methods (SHELXS-97) Sheldrick, 2008 were used for structure solution and refinement was carried out using SHELX-97 (Sheldrick, 2008), (full-matrix least-squares on F2). Hydrogen atoms were localized by difference electron density determination and refined using a riding model (H(N) free). An extinction correction was applied for **5b** and a semi-empirical absorption correction was applied for **6b**.

Compound **5b**: $C_{13}H_{13}N_3O_5S_2$, M = 355.38 g mol^{-1}, yellow crystals, crystal size 0.50 × 0.45 × 0.40 mm, orthorhombic, space group Pbca (No. 61), a = 13.8883(3) Å, b = 12.8134(4) Å, c = 16.8953(5) Å, V = 3006.63(14) Å3, Z = 8, D_{calcd} = 1.570 Mg m^{-3}, μ = 0.384 mm^{-1}, T = 123(2) K, 14529 reflection, 3424 unique [R_{int} = 0.019], $2\theta_{max}$ = 55°, 217 parameters, 2 restraints, R_1 [for 3198 $I > 2\sigma(I)$] = 0.028, wR_2 (all data) = 0.074, S = 1.12, largest diff. peak and hole = 0.385/−0.347 e A^{-3}.

Compound **6b**: $C_{14}H_{15}N_3O_3S$, Mr = 305.35 g mol^{-1}, yellow crystal, crystal size 0.50 × 0.30 × 0.20 mm, monoclinic, space group P21/n (No. 14), a = 7.3170(2) Å, b = 10.8893(3) Å, c = 17.6717(5) Å, β = 96.992(1) Å, V = 1397.56(7) A^{-3}, Z = 4, D_{calcd} = 1.451 Mg m^{-3}, μ = 0.246 mm^{-1}, T = 120(2) K, 11,545 reflection, 3144 unique [R_{int} = 0.012], $2\theta_{max}$ = 55°, 194 parameters, 1 restraint, R_1 [for 2967 $I > 2\sigma(I)$] = 0.028 WR_2 (all data) = 0.072, S = 1.04, largest diff. peak and hole = 0.370/−0.232 e A^{-3}.

Crystallographic data (excluding structure factors) for the structures reported in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 918764 (**5b**) and CCDC 918765 (**6b**). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge DB2 1EZ, UK (Fax: int.code + (1223)336-033; e-mail: deposit@ccdc.cam.ac.uk).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arabjc.2014.10.035.

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